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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YOUNG, JOSEPHINE	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/10/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,751	FISHMAN, PNINA	
	Examiner	Art Unit	
	Josephine Young	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003 and 27 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *1-9,13,14,19 and 22-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12,15-18,~~20,21~~ and 41-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8,9,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election of Species (b) in Paper No. 12, received November 21, 2002, is acknowledged. Because Applicant did not state that the election requirement was traversed and did not distinctly and specifically point out any supposed errors in the election requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, the examination of the claims is limited to the embodiments directed to nucleoside derivatives wherein Y is oxygen or sulfur.

Applicant's election with traverse of Group XI in Paper Nos. 14 and 15, mailed 11 March 2003 and 27 February 2003, respectively, is acknowledged. The traversal is on the ground(s) that Groups XI and XIII are linked by a common technical feature, namely methods of treating abnormal cell growth, such as cancer, using an A3RAg. However, as set forth in the Office Action, mailed January 28, 2003, KOHNO (1449, mailed April 29, 2002) teaches that adenosine A3 receptor agonists induce apoptosis in HL-60 human promyelocytic leukemia cells, and therefor has therapeutic value in the treatment of leukemia. See Abstract. Therefore, by 1996, methods to treat abnormal cell growth using adenosine A3 receptor agonists were known in the art. Thus, the technical feature linking the inventions of Groups XI and XIII, i.e. methods of treating abnormal cell growth, such as cancer, using an A3RAg, does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

Further, because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement with regard to the other Groups, the requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-9, 13, 14, 19 and 22-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The examination of linking claims 10-12, 15-18 and 20-21 is limited to the embodiments directed to methods to treat abnormal cell growth using an adenosine A3 receptor agonist. Similarly, the examination of linking claims 41-49 is limited to the embodiments directed to methods to treat abnormal cell growth using an adenosine A3 receptor agonist.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 10-12, 15-18, 20-21 and 41-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of lymphoma, melanoma and colon cancer, does not reasonably provide enablement for treating all forms of abnormal growth for all types of cells or for treating all types of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which cells or cancer lines would be effected by an adenosine A3 receptor agonist for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as only three different cell lines were assessed, out of the numerous known cell types and in particular the numerous cell types that are implicated in the various forms of cancers, malignancies, myeloid disorders, etc.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain agents and compositions are known to treat certain forms of cancer, no effective agent or composition has been found for the treatment of all cancer types. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compositions needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there are some working examples of the treatment of cancer related to lymphoma, melanoma and colon cancer, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 46 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In all occurrences, phrases referencing the meaning of a variable as defined in some alternative, preceding location, such as "above", without distinct reference to the particular location of said meaning or definition, renders the claim(s) in which said phrase(s) appear

indefinite. The reference to some alternative location for a definition is superfluous if the definition or meaning is already set forth in a claim or said definition or meaning is clearly set forth in an independent claim from which a claim depends. In all occurrences and under these circumstances, the phrases should be deleted from the claims as superfluous.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-11, 15-18, 20, 41-43 and 46-49 are rejected under 35 U.S.C. 102(b) as being anticipated by the article KOHNO *et al.*, Biochemical and Biophysical Research Communications, **1996**, *219*, 904-910 (1449, mailed April 29, 2002).

KOHNO teaches that adenosine A3 receptor agonists, such as N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (IB-MECA) and 2-chloro-N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (Cl-IB-MECA), induce apoptosis in HL-60 human promyelocytic leukemia cells, and therefor have therapeutic value in the treatment of leukemia. See Abstract. While KOHNO does not specifically state that the adenosine A3 receptor agonists would induce G-CSF production, these properties are inherent to the disclosed adenosine A3 receptor agonists since they are known to be of potential therapeutic value in the treatment of leukemia. The similar end uses envisioned for the adenosine A3 receptor agonists of KOHNO indicates similar mechanism of action. Therefore, though KOHNO does not

disclose any induction of G-CSF production, these are quantifications of inherent properties of the adenosine A3 receptor agonists. As the Office is not equipped to perform such testing, the burden of proof rests upon the applicant to show an actual difference in the properties observed.

The mere failure of a reference to disclose all the advantages asserted by applicant is not a substitute for actual differences in properties. In re DeBlauwe, 22 USPQ 191. An apparently old process cannot be converted into an unobvious one simply by the discovery of a characteristic one cannot glean from the cited prior art. Titanium Metals Corp. v. Banner, 227 USPQ 773.

Accordingly, the burden of proof is upon the Applicant to show that the instantly claimed subject matter is different from and unobvious over that taught by the prior art relied upon. In re Brown, 173 USPQ 65, 689; In re Best, 195 USPQ 430; In re Marosi, 21 USPQ 289, 293.

Claims 10-11, 15-16, 20, 41-43 and 46-47 are rejected under 35 U.S.C. 102(b) as being anticipated by the article MITTELMAN *et al.*, Annals New York Academy of Sciences, **1975**, *225*, 225-234 (1449, mailed April 29, 2002).

MITTELMAN teaches that N^6-(benzyladenosine) is a potent cytokinin and active in the mouse leukemia system. See page 225, last paragraph. While MITTELMAN does not specifically state that the N^6-(benzyladenosine) would induce G-CSF production, these properties are inherent to the disclosed N^6-(benzyladenosine) since they are known to be of potential therapeutic value in the treatment of leukemia. The similar end uses envisioned for the N^6-(benzyladenosine) of MITTELMAN indicates similar mechanism of action. Therefore, though MITTELMAN does not disclose any induction of G-CSF production, these are

quantifications of inherent properties of the N^6-(benzyladenosine). As the Office is not equipped to perform such testing, the burden of proof rests upon the applicant to show an actual difference in the properties observed.

The mere failure of a reference to disclose all the advantages asserted by applicant is not a substitute for actual differences in properties. In re DeBlauwe, 22 USPQ 191. An apparently old process cannot be converted into an unobvious one simply by the discovery of a characteristic one cannot glean from the cited prior art. Titanium Metals Corp. v. Banner, 227 USPQ 773.

Accordingly, the burden of proof is upon the Applicant to show that the instantly claimed subject matter is different from and unobvious over that taught by the prior art relied upon. In re Brown, 173 USPQ 65, 689; In re Best, 195 USPQ 430; In re Marosi, 21 USPQ 289, 293.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10-12, 15-18, 20-21 and 41-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over KOHNO in view of patent US 5,688,774 to JACOBSON et al. (1449, mailed April 29, 2002).

Applicant claims the use of various adenosine A3 receptor agonists to treat abnormal cellular proliferation, and in a particular embodiment administered orally. Further, Applicant claims the use of adenosine A3 receptor agonists in combination with a chemotherapeutic drug.

As set forth supra, KOHNO teaches that adenosine A3 receptor agonists, such as N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (IB-MECA) and 2-chloro-N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (Cl-IB-MECA), induce apoptosis in HL-60 human promyelocytic leukemia cells, and therefor have therapeutic value in the treatment of leukemia.

KOHNO does not specifically teach that the adenosine A3 receptor agonists, N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (IB-MECA) and 2-chloro-N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (Cl-IB-MECA), can be administered orally or in combination with a chemotherapeutic drug.

JACOBSON teaches the use of adenosine A3 receptor agonists in the regulation of CNS, cardiac inflammatory and reproductive functions. See column 3, lines 45-67. Further, JACOBSON discloses that the therapeutically effective adenosine A3 receptor agonists can be administered orally (column 10, lines 29-57).

It would have been obvious to one of ordinary skill in the art to administer the adenosine A3 receptor agonists of KOHNO orally, as JACOBSON teaches that such compounds are easily

formulated for oral administration. Further, since KOHNO teaches that the adenosine A3 receptor agonists have therapeutic value in the treatment of leukemia, and combination therapies are standard in the art of cancer therapeutics, a skilled artisan would have been motivated and had a reasonable expectation of success for treating leukemia using an adenosine A3 receptor agonist of KOHNO in combination with one or more other known chemotherapeutic agent.

Claims 10-12, 15-18, 20-21 and 41-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over KOHNO and International Patent Publication WO 99/02143 to CAN-FITE TECHNOLOGIES LTD. (1449, mailed April 24, 2001) in view of patent US 5,688,774 to JACOBSON.

Applicant claims the use of various adenosine A3 receptor agonists to treat abnormal cellular proliferation. Further, Applicant claims the use of adenosine A3 receptor agonists in combination with a chemotherapeutic drug. Applicant also claims methods to treat cancer by administering an adenosine A3 receptor agonist that also counters the toxic side effects of a chemotherapeutic drug, optionally providing a stronger synergistic effect. Finally, Applicant claims methods wherein the adenosine A3 receptor agonist is administered orally.

As set forth supra, KOHNO teaches that adenosine A3 receptor agonists, such as N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (IB-MECA) and 2-chloro-N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (Cl-IB-MECA), induce apoptosis in HL-60 human promyelocytic leukemia cells, and therefor have therapeutic value in the treatment of leukemia.

KOHNO does not specifically teach that the adenosine A3 receptor agonists, N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (IB-MECA) and 2-chloro-N^6—(3-iodobenzyl)adenoisne-5'-N-methylcarboxamide (Cl-IB-MECA), can be administered orally or in combination with a chemotherapeutic drug. Further, KOHNO does not explicitly state that such adenosine A3 receptor agonists would be able to counter the toxic side effects of a chemotherapeutic drug or would have a strong synergistic effect with such chemotherapeutic drug.

CAN-FITE teaches that adenosine has an effect in inducing proliferation of bone marrow cells, resulting in increase in the number of leukocytes and particularly of neutrophils in the peripheral blood, thereby exhibiting a protective effect against some toxic effect of chemotherapeutic drugs. See page 6, lines 6-17. Further, on that same page, lines 28-25, CAN-FITE discloses that the overall effect of adenosine when administered together with a chemotherapeutic drug is an increase in the therapeutic index, namely by reducing the toxic side effects and improving specific activity. CAN-FITE further extrapolates that such an effect can be achieved using agents that interact with the adenosine system. "In addition, as will no doubt be appreciated by the artisan, although the use of adenosine is preferred in accordance with the invention, other nucleosides as well as nucleoside derivatives may potentially be used to obtain qualitatively similar effects to that of adenosine." See page 7, lines 5-29.

JACOBSON teaches the use of adenosine A3 receptor agonists in the regulation of CNS, cardiac inflammatory and reproductive functions. See column 3, lines 45-67. Further, JACOBSON discloses that the therapeutically effective adenosine A3 receptor agonists can be administered orally (column 10, lines 29-57).

Since KOHNO teaches that the adenosine A3 receptor agonists have therapeutic value in the treatment of leukemia, and combination therapies are standard in the art of cancer therapeutics, a skilled artisan would have been motivated and had a reasonable expectation of success for treating leukemia using an adenosine A3 receptor agonist of KOHNO in combination with one or more other known chemotherapeutic agent. Further, it would have been obvious to one of ordinary skill in the art that the adenosine derivatives of KOHNO could also induce the proliferation of bone marrow cells, resulting in an increase in the number of leukocytes and particularly of neutrophils in the peripheral blood, thereby exhibiting a protective effect against some toxic effect of chemotherapeutic drugs, as per CAN-FITE. Therefore, a skilled artisan would have been motivated and had a reasonable expectation of success for using the adenosine A3 receptor agonists of KOHNO to treat cancer with the dual effect of inhibiting proliferation of cancer cells and countering the toxic side effects of chemotherapeutic drug treatment. Finally, it would have been obvious to one of ordinary skill in the art to administer the adenosine A3 receptor agonists of KOHNO orally, as JACOBSON teaches that such compounds are easily formulated for oral administration.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-56 are pending. Claims 1-9, 13, 14, 19 and 22-40 are withdrawn. Claims 10-12, 15-18, 20-21 and 41-56 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
June 2, 2003

JAMES O. WILSON
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